

**Memorandum**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

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**FROM:** LCDR David Moeny, R.Ph. USPHS, Pharmacist / Drug Use Specialist  
Judy A. Staffa, Ph.D., R.Ph., Epidemiology Team Leader  
Division of Surveillance, Research and Communication Support, HFD-410

**THROUGH:** Gerald Dal Pan, MD, MHS. Director  
Division of Surveillance, Research and Communication Support, HFD-410

**TO:** Solomon Iyasu, MD, MPH  
Div. of Pediatric Drugs and Development, HFD-960  
Office of Counter-Terrorism and Pediatric Development

**SUBJECT:** One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data Fluconazole (Diflucan<sup>®</sup>) Oral Suspension: NDA 21-718

**\*\*This document contains proprietary data from IMS Health, Caremark, and Premier which cannot be shared outside of FDA without clearance from IMS Health, Caremark, and Premier obtained through the Office of Drug Safety.\*\***

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**EXECUTIVE SUMMARY**

This consult examines drug utilization trends for oral preparations of fluconazole (Diflucan<sup>®</sup>) in the pediatric population (ages 0-16 years). Sales data were examined for the four-year period from February 1, 2001 – January 31, 2005 with a primary focus on sales patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Diflucan<sup>®</sup> oral suspension on January 21, 2004. Outpatient drug utilization patterns were examined for the 3-year period from February 1, 2002 – January 31, 2005 with a primary focus on utilization patterns during the year before and after the granting of pediatric exclusivity. Inpatient use patterns were examined for the 6 months before and after the granting of exclusivity; a 1 year period from August 1, 2003 to July 31, 2004. The oral antifungals included in this analysis were fluconazole, itraconazole, voriconazole, terbinafine, and ketoconazole. Since approximately 30% of all fluconazole sales are into the non-retail channels, both inpatient and outpatient drug utilization patterns will be addressed.

Outpatient prescriptions of selected oral antifungal products combined increased by 4% over the period of February 2002 – January 2005. Fluconazole was the most commonly dispensed product compared to the other antifungal products in this analysis, accounting for 11.1 million yearly prescriptions dispensed during February 2002 – January 2003 and 11.4 million prescriptions dispensed during February 2004 – January 2005, a 3% relative increase.

Prescriptions for brand name Diflucan declined by 42% from 11.2 million prescriptions dispensed in the pre-exclusivity year (February 2003 – January 2004) to 6.4 million prescriptions dispensed in the post-exclusivity year (February 2004 – January 2005). This large decline is primarily due to the introduction of generic fluconazole products which were approved for marketing in July and August of 2004 and accounted for 44% of combined fluconazole dispensing during the final year of this analysis (February 2004 – January 2005).

Fluconazole oral suspension accounted for 3% of all fluconazole prescriptions dispensed in each year during February 2002 – January 2005. Prescriptions dispensed for fluconazole suspension increased from 322,000 prescriptions dispensed in February 2002 – January 2003 to 336,000 prescriptions dispensed during February 2004 – January 2005. Generic products accounted for 33% of fluconazole suspension dispensing in the last year of this analysis.

The top two prescriber specialties prescribing oral fluconazole from January 2002 through February 2005 were pediatrics and family practice. Of all specialties, pediatricians were ranked 1<sup>st</sup> in prescribing oral fluconazole suspension and accounted for 62-63% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for fluconazole oral suspension dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

Among an insured patient population whose prescription claims are managed by Caremark, pediatric patients age 1-16 years accounted for approximately 91% of the claims for fluconazole oral suspension (brand and generic combined) in each of the three one-year periods from February 2002 – January 2005. Among pediatric patients ages 1-16 years, use was highest in 1 year old patients who accounted for 71-72% of fluconazole oral suspension claims during February 2002 – January 2005. Based on estimates applying Caremark proportions to IMS Health national prescription estimates, the estimated nationwide prescriptions for fluconazole oral suspension in patients age 1-16 years increased by 1.1%, rising from 303,000 prescriptions during the year before granting the exclusivity (February 2003- January 2004) to 307,000 prescriptions in the year after the granting of exclusivity (February 2004 – January 2005).

The most common diagnosis for pediatric patients ages 0-16 years associated with a mention of fluconazole oral suspension in office based physician-patient encounters was “neonatal candida infection” which accounted for 44% of mentions during the pre-exclusivity period (February 2003 – January 2004) and 57% of mentions during the post-exclusivity (February 2004 – January 2005) period. The use in the adult population ages 17 years and over was too low to analyze.

In a database of 450 acute care hospitals, there were 1,541 actual discharges associated with a charge for fluconazole oral suspension during the 6 months prior to the granting of exclusivity (August 2003 – January 2004) and 1,286 discharges in the 6 months following the granting of exclusivity (February 2004 – July 2004). This represents a 17% relative decrease in fluconazole use. Pediatric patients ages 0 – 16 years accounted for 670 discharges (43%) in the pre-

exclusivity period and 496 discharges (39%) in the post-exclusivity period, a relative 26% decrease.

In a subset of 37 pediatric hospitals and care centers, discharges associated with a charge for fluconazole oral suspension declined by 31% from 420 discharges during the 6 months prior to exclusivity (August 2003 – January 2004) to 290 discharges during the 6 months after exclusivity (February 2004 – August 2004). Similar to the outpatient setting, patients age 1 year old and under were most commonly associated with a charge for fluconazole oral suspension, accounting for 56% of discharges during the post-exclusivity period.

In summary, use of oral fluconazole suspension is concentrated in 1 year old patients who represent approximately 64% of overall outpatient usage and 25% of overall inpatient usage. Estimated pediatric outpatient prescriptions increased by 1% from the pre to post exclusivity years while inpatient discharges decreased by 26% from the 6 months post exclusivity to the 6 months following exclusivity.

## **INTRODUCTION**

On February 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Fluconazole (Diflucan<sup>®</sup>), the first of a new subclass of synthetic triazole antifungal agents, is available as tablets for oral administration (NDA 19-949), as a powder for oral suspension (NDA 21-718) and as a sterile solution for intravenous use (NDA 19-950).

The oral antifungals included in this analysis are fluconazole, itraconazole, voriconazole, terbinafine, and ketoconazole, since all of these products are available in oral dosage forms, and used for systemic fungal infections. We did not examine the use of nystatin and amphotericin B since these products are either not typically used for systemic infection (nystatin) or administered orally (amphotericin B).

### Indications and Usage<sup>1</sup>

Experience with Diflucan in neonates is limited to pharmacokinetic studies in premature newborns. Based on the prolonged half-life seen in premature newborns (gestational age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as older children, but administered every 72 hours. After the first two weeks, these children should

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<sup>1</sup> Indications, use, and dosage were taken from the manufacturer's product labeling approved August 2004

be dosed once daily. No information regarding Diflucan pharmacokinetics in full-term newborns is available.

**Oropharyngeal candidiasis:** The recommended dosage of Diflucan for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

**Esophageal candidiasis:** For the treatment of esophageal candidiasis, the recommended dosage of Diflucan in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.

**Systemic Candida infections:** For the treatment of candidemia and disseminated Candida infections, daily doses of 6-12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

**Cryptococcal meningitis:** For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of Diflucan is 6 mg/kg once daily.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Diflucan<sup>®</sup> oral suspension (NDA 21-718) on January 21, 2004.

This review describes both outpatient and inpatient drug usage of Diflucan<sup>®</sup> oral suspension in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

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## **DATA SOURCES**

This review describes the annual sales and drug use patterns of Diflucan<sup>®</sup> oral suspension in the pediatric population as compared to the adult population in several years before and one year after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

### ***Outpatient Drug Usage***

#### ***IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)***

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions.

These retail pharmacies include chain, independent, food store, mail order, discount houses,

and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed for oral antifungal preparations in the allylamine, imidazole and imidazole classes from February 1, 2002 - January 31, 2005 inclusive, with emphasis on Diflucan<sup>®</sup> and generic fluconazole products.

### ***IMS HEALTH, NATIONAL SALES PERSPECTIVES™***

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections. The oral antifungals included in this analysis are fluconazole, itraconazole, voriconazole, terbinafine, and ketoconazole; nystatin and amphotericin B were not included.

For this analysis, the sales trend of oral fluconazole and the selected oral antifungals were examined from February 1, 2001 - January 31, 2005, inclusive

### ***CAREMARK***

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million participants, and processing over 545 million prescription claims annually. FDA has access to Caremark's Dimension Rx™ database consisting of a subset of total Caremark paid claims representing 350 million claims per year for prescriptions filled in 57,000 pharmacies across the country. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's Dimension Rx™ system includes participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark's Dimension Rx™ system to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims of Diflucan<sup>®</sup> and generic fluconazole suspension in the Caremark system were examined from February 1, 2002 - January 31, 2005 inclusive.

### ***IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)***

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of Diflucan® and fluconazole generic suspension during office-based physician visits during the time period from February 1, 2001 - January 31, 2005 inclusive.

### ***Inpatient Drug Usage***

#### ***PREMIER™***

Premier maintains a large hospital drug utilization and financial database. The database contains information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database. Data are available from January 2000 through the present, but have a lag time of approximately six months. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, Premier developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to the database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, we believe that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommend making this determination on a drug-specific basis. For fluconazole, we did not use projected estimates, given the very competitive marketplace for these products getting on a hospital formulary, and therefore the possibility that hospitals with Premier purchasing agreements may not be truly representative of hospitals

nationwide. Rather the Premier data provides a glimpse of practice in approximately 450 acute, short-stay hospitals.

For this analysis, the total number of distinct discharges within Premier hospitals which included claims for fluconazole oral suspension was examined for the 6 months before and after the granting of exclusivity; a one year time period from August 1, 2003 to July 31, 2004, inclusive.

### ***PREMIER PEDIATRIC™***

Premier's pediatric database represents a subset of information from 37 pediatric hospitals. In addition, Premier maintains data on all pediatric discharges from the larger sample of approximately 450 acute care facilities. Overall, the pediatric population in Premier's pediatric database includes greater than 3 million inpatient records. Data are available from January 2000 through the present, but have a lag time of approximately six months.

For this analysis, the total number of distinct discharges associated with fluconazole oral suspension use within these 37 tertiary care pediatric hospitals was examined for the 6 months before and after the granting of exclusivity; a one year time period from August 1, 2003 to July 31, 2004, inclusive.

## **RESULTS**

### **I. Sales and Distribution Channels**

Sales of fluconazole (Diflucan<sup>®</sup> and generic fluconazole) were examined from February 1, 2001 – January 31, 2005 (Table 1). Retail channels are the largest purchasers of the tablet and suspension dose forms, representing at least 91% of the bottles of tablets and at least 80% of the bottles of suspension sold in each of the four one-year periods of this analysis while non-retail channels accounted for nearly 100% of injectable fluconazole sales during the same periods. Total sales of oral and injectable fluconazole dosage forms combined increased by a relative 9% over the 4 years of this analysis from 7.5 million bottles and bags sold during February 2001 – January 2002 to 8.2 million bottles and bags sold during February 2004 – January 2005. Compared to the pre-exclusivity period (February 2003 – January 2004), total sales of fluconazole in the post exclusivity period (February 2004 – January 2005) increased by 5% from 7.8 million bottles and bags to 8.2 million bottles and bags sold. Sales of fluconazole suspension increased by 26% over the 4 years of this analysis from 441,000 bottles sold in February 2001 – January 2002 to 557,000 bottles sold in February 2004 – January 2005. Compared to the pre-exclusivity period (February 2003 – January 2004), total sales of fluconazole suspension in the post exclusivity period (February 2004 – January 2005) increased by 12% from 497,000 bottles to 557,000 bottles sold.

**Table 1. Total Number of bottles (suspension, tablets) or bags (injectable) of Fluconazole (Diflucan<sup>®</sup> brand and generic) Sold to U.S. Distribution Channels During February 2001 – January 2005 (in thousands)**

	February 2001 - January 2002		February 2002 - January 2003		February 2003 - January 2004		February 2004 - January 2005	
	N (%) <sup>†</sup>		N (%)		N (%)		N (%)	
<b>Fluconazole</b>	<b>7,532</b>	<b>100%</b>	<b>7,738</b>	<b>100%</b>	<b>7,821</b>	<b>100%</b>	<b>8,239</b>	<b>100%</b>
<b>Tablets</b>	<b>4,850</b>	<b>64%</b>	<b>4,890</b>	<b>63%</b>	<b>4,947</b>	<b>63%</b>	<b>5,496</b>	<b>67%</b>
<b>Retail</b>	4,463	92%	4,483	92%	4,509	91%	5,024	91%
<b>Non-retail</b>	388	8%	407	8%	439	9%	472	9%
<b>Injectable</b>	<b>2,240</b>	<b>30%</b>	<b>2,384</b>	<b>31%</b>	<b>2,376</b>	<b>30%</b>	<b>2,186</b>	<b>27%</b>
<b>Retail</b>	4	0%	6	0%	5	0%	5	0%
<b>Non-retail</b>	2,236	100%	2,378	100%	2,371	100%	2,181	100%
<b>Suspension</b>	<b>441</b>	<b>6%</b>	<b>464</b>	<b>6%</b>	<b>497</b>	<b>6%</b>	<b>557</b>	<b>7%</b>
<b>Retail</b>	355	81%	370	80%	400	80%	459	82%
<b>Non-retail</b>	86	19%	94	20%	98	20%	99	18%

\*Retail includes chain, independent, mail order, food store pharmacies

\*\* Non-retail includes Non-federal hospitals, federal facilities, long term care, clinics, HMOs, home health care, prisons, universities, and other

<sup>†</sup>Subtotals may not sum exactly due to rounding error

IMS Health, National Sales Perspectives™ Combined, February 2001 – January 2005, Data Extracted 03-2005 (File:0503flu6.xls)

## II. Outpatient Data

### Dispensed Prescriptions

Outpatient prescriptions of the selected oral antifungal agents combined increased by approximately 4% during February 2002 – January 2005, rising from 14.8 million prescriptions dispensed in the 12-month period from February 2002 – January 2003 to 15.4 million prescriptions in the 12-month period from February 2004 – January 2005 (Table 2). During February 2004 through January 2005, fluconazole products accounted for 75% (11.4 million prescriptions) of the combined oral antifungal market with terbinafine and ketoconazole accounting for 17% (2.7 million prescriptions) and 5% (740,000 prescriptions) respectively.

Prescriptions for all oral fluconazole products combined increased by 3% over the three 1 year periods of this analysis with 11.1 million prescriptions dispensed during February 2002 – January 2003, 11.2 million prescriptions dispensed during February 2003 – January 2004, and 11.4 million prescriptions dispensed during February 2004 – January 2005. Prescriptions for brand name Diflucan<sup>®</sup> declined by 42% from 11.2 million prescriptions dispensed in the pre-exclusivity year (February 2003 – January 2004) to 6.4 million prescriptions dispensed in the post-exclusivity year (February 2004 – January 2005). This large decline is primarily due to the introduction of generic fluconazole products which were approved for marketing in July and August 2004 and accounted for 44% of combined brand and generic fluconazole dispensing during the final year of this analysis (February 2004 – January 2005).

Fluconazole oral suspension accounted for 3% of prescriptions dispensed in each year, and prescription volume increased in each year with 322,000 prescriptions dispensed in February 2002 – January 2003, 335,000 prescriptions dispensed during February 2003 – January 2004,

and 336,000 prescriptions dispensed during February 2004 – January 2005; a relative increase of 4%. Generic products accounted for 33% of fluconazole suspension dispensing in the last year of this analysis.

**Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Oral Anti-Fungal Products During February 2002 – January 2005**

	February 2002 - January 2003		February 2003 - January 2004		February 2004 - January 2005	
	N <sup>†</sup> (000)	(%)	N (000)	(%)	N (000)	(%)
<b>Selected Oral Antifungals</b>	<b>14,824</b>	<b>(100)</b>	<b>15,013</b>	<b>(100)</b>	<b>15,352</b>	<b>(100)</b>
<b>Fluconazole</b>	<b>11,070</b>	<b>(75)</b>	<b>11,192</b>	<b>(75)</b>	<b>11,448</b>	<b>(75)</b>
<i>Diflucan</i>	11,070	(100)	11,192	(100)	6,436	(56)
<i>Tablets</i>	10,748	(97)	10,857	(97)	6,210	(96)
<i>Suspension</i>	322	(3)	335	(3)	226	(4)
<i>Fluconazole Generic</i>	-	(0)	-	(0)	5,012	(44)
<i>Tablets</i>	-		-		4,903	(98)
<i>Suspension</i>	-		-		110	(2)
<b>Terbinafine</b>	<b>2,406</b>	<b>(16)</b>	<b>2,551</b>	<b>(17)</b>	<b>2,678</b>	<b>(17)</b>
<b>Ketoconazole</b>	<b>715</b>	<b>(5)</b>	<b>720</b>	<b>(5)</b>	<b>740</b>	<b>(5)</b>
<b>Itraconazole</b>	<b>626</b>	<b>(5)</b>	<b>520</b>	<b>(4)</b>	<b>443</b>	<b>(4)</b>
<b>Voriconazole</b>	<b>7</b>	<b>(0)</b>	<b>30</b>	<b>(0)</b>	<b>42</b>	<b>(0)</b>

IMS Health, NPA Plus™ February 2002 – January 2005, data extracted 1-2005 (File: 0503flu2.dvr)

<sup>†</sup>Subtotals may not sum exactly due to rounding error

### Prescriber specialty

The top two prescriber specialties prescribing oral fluconazole suspension from January 2002 through February 2005 were pediatrics and family practice (Table 3). Of all specialties, pediatricians were ranked 1<sup>st</sup> in prescribing oral fluconazole suspension during this period and accounted for 62-63% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for oral fluconazole suspension<sup>®</sup> dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

**Table 3: Total Number of Prescriptions Dispensed for Fluconazole Oral Suspension Nationwide by Physician Specialty During February 2002 – January 2005 (excludes Mail Order and Long Term Care)**

Prescriber Specialty	February 2002 - January 2003		February 2003 - January 2004		February 2004 - January 2005	
	N (%)		N (%)		N (%)	
<b>All Prescribers</b>	<b>311,209</b>		<b>325,078</b>		<b>324,498</b>	
Pediatrics	194,067	(62)	205,012	(63)	204,024	(63)
Family Practice	28,012	(9)	29,047	(9)	28,760	(9)
Osteopathic Medicine	15,888	(5)	16,345	(5)	16,075	(5)
Others(67)	73,242	(24)	74,674	(23)	75,639	(23)

IMS Health NPA Plus™, February 2002 – January 2005, Data extracted 03-2005 (file: 0503flu3.xls)

### Patient Demographics

Among a large, insured patient population whose prescription drugs benefits are managed by Caremark, pediatric patients age 1-16 years accounted for approximately 91% of the claims for fluconazole oral suspension (brand and generic) in each of the three one-year periods from February 2002 – January 2005 (Table 4). Among pediatric patients ages 1-16 years, use was highest in 1 year old patients who accounted for approximately 71% of fluconazole oral suspension claims during February 2002 – January 2005.

**Table 4. Percentage of Paid Prescription Claims for Fluconazole Oral Suspension Processed by Caremark during February 2002 – January 2005**

	February 2002 - January 2003	February 2003 - January 2004	February 2004 - January 2005
<b>Age 1-16</b>	<b>90.4%</b>	<b>90.5%</b>	<b>91.4%</b>
Age 1	72.0%	71.5%	70.5%
Age 2-11	27.0%	27.6%	28.5%
Age 12-16	1.0%	0.9%	1.0%
<b>Age 17+</b>	<b>9.6%</b>	<b>9.5%</b>	<b>8.6%</b>

Caremark Dimension Rx™-Data Extracted 1-2005 (file: Caremark Fluconazole 3-2005.xls)

<sup>1</sup>Subtotals may not sum exactly due to rounding error

Applying the percentages of claims for fluconazole oral suspension obtained from Caremark (Table 4) to the total projected prescriptions filled nationwide obtained from IMS (Table 2), allowed us to estimate the total number of prescriptions filled nationwide for pediatric patients (Table 5). The estimated nationwide prescriptions for fluconazole oral suspension in patients age 1-16 years increased by 1.1%, rising from 303,208 prescriptions during the year before granting the exclusivity (February 2003- January 2004) to 306,579 prescriptions in the year after the granting of exclusivity (February 2004 – January 2005). Within the pediatric age group, the estimated prescriptions for the 12-16 years old subgroup exhibited the largest increase during the

same time period, rising by 12% from 2,729 estimated prescriptions dispensed during February 2003 – January 2004 to 3,066 estimated prescriptions dispensed during February 2004 – January 2005.

**Table 5. Estimated Nationwide Prescriptions\* Filled for Diflucan<sup>®</sup> Suspension and Generic Fluconazole Suspension during February 2002 – January 2005**

	<b>February 2002 - January 2003</b>	<b>February 2003 - January 2004</b>	<b>February 2004 - January 2005</b>
<b>Total Prescriptions**</b>	<b>322,175</b>	<b>335,036</b>	<b>335,426</b>
<b>Age 1-16</b>	<b>291,246</b>	<b>303,208</b>	<b>306,579</b>
<i>Age 1</i>	209,697	216,794	216,138
<i>Age 2-11</i>	78,636	83,685	87,375
<i>Age 12-16</i>	2,912	2,729	3,066
<b>Age 17+</b>	<b>30,929</b>	<b>31,828</b>	<b>28,847</b>

\* Estimated number of prescriptions in each age band obtained by applying percentages in each age band obtained from Caremark to IMS Health’s total prescriptions.

\*\* Total Prescriptions are actual values from IMS Health (Table2)

The most common diagnosis for pediatric patients ages 0-16 years associated with a mention of fluconazole oral suspension in office based physician-patient encounters was “neonatal candida infection” (ICD-9 771.7) which accounted for 44% of mentions during the pre-exclusivity period (February 2003 – January 2004) and 57% of mentions during the post-exclusivity (February 2004 – January 2005) period (Table 6). Due to the low number of visits in the adult population, we were unable to complete an analysis of this subgroup.

**Table 6. Top Diagnoses Associated with Mentions of Diflucan® and Fluconazole Generic Oral Suspension Combined During February 2002 - January 2005**

IMS reported ICD-9 Diagnosis Code	February 2002 - January 2003		February 2003 - January 2004		February 2004 - January 2005	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<b>Total All Patients</b>	212,400	(100.0)	129,399	(100.0)	168,392	(100.0)
<b>Age 0 - 16</b>	193,634	(91.2)	105,235	(81.3)	165,366	(98.2)
<b>771.7 Neonatal Candida Infectn</b>	118,370	(61.1)	46,493	(44.2)	94,020	(56.9)
<b>112.0 Candidiasis Of Mouth</b>	37,950	(19.6)	35,554	(33.8)	27,275	(16.5)
<b>112.9 Candidiasis Unsp Sites</b>	7,964	(4.1)	---	---	11,168	(6.8)
<b>V675 Exam Follow Oth Treatmen</b>	7,912	(4.1)	---	---	9,521	(5.8)
<b>117.9 Mycoses Other &amp; Unspec</b>	---	---	---	---	8,381	(5.1)
<b>112.1 Candidiasis Vulva+Vagina</b>	---	---	15,781	(15.0)	5,891	(3.6)
<b>171.9 Mal Neo Site Uns Con Tis</b>	1,917	(1.0)	---	---	2,225	(1.3)
<b>799.9 Unk+Unspec Cause Oth</b>	---	---	---	---	1,876	(1.1)
<b>V429 Unsp Organ/Tiss Transpl.</b>	---	---	---	---	1,748	(1.1)
<b>204.0 Acute Lymphoid Leukemia</b>	4,709	(2.4)	---	---	1,748	(1.1)
<b>Total Others (5)</b>	14,812	(7.6)	7,407	(7.0)	1,513	(0.9)
<b>Age 17 +</b>	18,766	(8.8)	6,665	(5.2)	---	---
<b>112.0 Candidiasis Of Mouth</b>	16,849	(89.8)	1,215	(18.2)	---	---
<b>112.9 Candidiasis Unsp Sites</b>	---	---	4,125	(61.9)	---	---
<b>161.9 Mal Neo Larynx Unsp</b>	---	---	1,325	(19.9)	---	---
<b>200.0 Reticulosarcoma</b>	1,917	(10.2)	---	---	---	---
<b>Total Others (0)</b>	---	---	---	---	---	---
<b>Unspecified</b>	---	---	17,499	(13.5)	3,026	(1.8)

IMS National Disease and Therapeutic Index™, MAT 3 year February 2002 - January 2004. Data extracted 3-2005 (File NDTI Fluconazole Diags 3-2005.dvw)

### III. Inpatient Drug Use Data

Utilizing Premier's database of 450 acute care hospitals, there were 1,541 actual discharges associated with a charge for any fluconazole oral suspension during the 6 months prior to the granting of exclusivity (August 2003 – January 2004) and 1,286 discharges in the 6 months following the granting of exclusivity (February 2004 – July 2004) (Table 7). This represents a 17% relative decrease in fluconazole use. Pediatric patients ages 0 – 16 years accounted for 670 discharges (43%) in the pre-exclusivity period and 496 discharges (39%) in the post-exclusivity period, a 26% decrease.

**Table 7. Premier Network Acute Care Hospital Discharges Associated with a Charge for Fluconazole Oral Suspension for the 6 months before and after exclusivity (Aug 2003 – July 2004)**

	August 2003 - January 2004		February 2004 - July 2004	
	Number of Actual Discharges			
	N <sup>†</sup> (%)		N (%)	
<b>Total</b>	<b>1541</b>		<b>1286</b>	
Age 0-16	670	(43)	496	(39)
Age 0-1	406	(61)	311	(63)
Age 2-11	231	(34)	147	(30)
Age 12-16	33	(5)	38	(8)
Age 17+	871	(57)	790	(61)

Source: Premier Informatics Extracted 3-25-05 file

(Premier Fluconazole Strength by Age all hosp.xls)

<sup>†</sup>Subtotals may not sum correctly due to rounding error

In a subset of 37 Premier Network pediatric hospitals and care centers, discharges associated with a charge for any fluconazole oral suspension declined by 31% from 420 discharges during the 6 months prior to exclusivity (August 2003 – January 2004) to 290 discharges during the 6 months after exclusivity (February 2004 – August 2004) (Table 8). Similar to the larger group of hospitals, patients under the age of 2 years were most commonly associated with a charge for fluconazole oral suspension, accounting for 56% of discharges during the post-exclusivity period.

**Table 8. Premier Network Pediatric Care Center Discharges Associated with a Charge for Fluconazole Oral Suspension for the 6 months before and after exclusivity (Aug 2003 – July 2004)**

	August 2003 - January 2004		February 2004 - August 2004	
	Number of Actual Discharges			
	N (%)		N (%)	
<b>Age 0-16</b>	<b>420</b>		<b>290</b>	
Age 0-1	221	(52)	163	(56)
Age 2-11	174	(41)	102	(35)
Age 12-16	25	(6)	25	(9)

Source: Premier Informatics Extracted 3-25-05 file

(Premier Fluconazole Strength by Age peds hosp.xls)

<sup>†</sup>Subtotals may not sum correctly due to rounding error

## DISCUSSION

### Sales data

The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these

products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

### Outpatient use

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not prevalent, as in the case of fluconazole suspension in the adult population.

Caremark data cannot be projected to provide national estimates, but its large sample size can be helpful for replicating demographic findings in IMS Health's NDTI™, where sample sizes are often small. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations based on the proportion dispensed to pediatric patients in the Caremark system and are dependent upon the assumption that these patterns are similar across populations with and without prescription drug coverage. The accuracy of this assumption is not known at this time. In addition, reliable information for patients less than the age of 1 year is not available from this data source.

### Inpatient use

The inpatient data from Premier, while providing a helpful view of the use of oral fluconazole suspension in the hospital setting, cannot be projected to provide nationwide estimates of the use of this product in children hospitalized throughout the U.S. Although the use of fluconazole within the large sample of general hospitals (~450 hospitals) and the smaller sample of children's hospitals and care centers (37 hospitals and centers) is informative, an appropriate method for projecting these estimates is not yet available.

## **CONCLUSION**

Outpatient prescriptions for oral antifungal agents overall increased by 4% from February 2002 – January 2005, while prescriptions for fluconazole oral products increased by 3% during this same period. Prescriptions for brand name Diflucan® decreased by 42% in the final year of this analysis (February 2004 – January 2005), due primarily to the introduction of generic products in July and August of 2004. Generics accounted for 44% of prescriptions filled for oral fluconazole products during February 2004 through January 2005. Pediatric patients ages 1-16 years were more likely to be dispensed fluconazole oral suspension, accounting for an estimated 307,000

prescriptions during February 2004 – January 2005, compared to 29,000 prescriptions filled during the same period for patients age 17 years and older. This trend was consistent in each of the 3 years of this analysis.

In general, prescribing patterns for fluconazole dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period. The use of this product appears to be primarily in the pediatric population (ages 1-16 years) which accounted for roughly 91% of paid claims processed by Caremark in each of the 3 years of this analysis. Among pediatric patients, children age 1 year old accounted for 71-72% of yearly paid oral fluconazole suspension claims processed by Caremark.

The top two prescriber specialties prescribing oral fluconazole suspension from January 2002 through February 2005 were pediatrics and family practice. Of all specialties, pediatricians were ranked first in prescribing oral fluconazole suspension during this period and accounted for 62-63% of the prescriptions dispensed in each of the 3 one-year periods of this analysis

The most common diagnosis for pediatric patients ages 0-16 years associated with a mention of fluconazole oral suspension in office based physician-patient encounters was “neonatal candida infection” which accounted for 44% of mentions during the pre-exclusivity period (February 2003 – January 2004) and 57% of mentions during the post-exclusivity (February 2004 – January 2005) period.

In summary, use of oral fluconazole suspension is concentrated in the youngest patients with 1 year olds who representing approximately 64% of overall outpatient usage and patients 0-1 years old representing roughly 25% of overall inpatient usage. Estimated pediatric outpatient prescriptions increased by 1% from the pre to post exclusivity years while inpatient discharges decreased by 26% from the 6 months post exclusivity to the 6 months following exclusivity.

**LCDR David Moeny, USPHS, R.Ph.  
Pharmacist/Drug Utilization Data Specialist  
Division of Surveillance, Research, and  
Communication Support (DSRCS)**

**Judy A. Staffa, Ph.D., R.Ph.  
Epidemiology Team Leader  
Division of Surveillance, Research, and  
Communication Support (DSRCS)**

**Laura Governale, Pharm D., MBA.  
Team Leader  
Division of Surveillance, Research, and  
Communication Support (DSRCS)**

**Gerald Dal Pan, M D, MHS  
Division Director  
Division of Surveillance, Research, and  
Communication Support (DSRCS)**